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(54) Title: METHODS AND COMPOSITIONS FOR TREATMENT OF HEPATITIS C INFECTION

## (57) Abstract

Methods and compositions useful for treatment of hepatitis C infection are disclosed. In general, the compositions comprise a composition comprising at least two compounds selected from the group consisting of a nucleoside analog, a quinolone antibiotic, and an amantadine anti-viral agent. The compositions or drug combinations can optionally include an interferon, such as interferon  $\alpha$ . Pharmaceutical compositions and kits including the compositions of the invention are also disclosed.

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## METHODS AND COMPOSITIONS FOR TREATMENT OF HEPATITIS C INFECTION

### Background of the Invention

Chronic hepatitis C is a world-wide epidemic. In the United States, an estimated four million people are infected with hepatitis C. In other countries, as much as 10 percent or more of the population is affected. Hepatitis C is a major cause of cirrhosis of the liver and liver cancer. Liver cancer is a leading cause of cancer deaths world-wide. It is generally accepted that the best measure of cure of hepatitis C is the eradication of the virus in the infected person. Treatments that lead to normalization of liver enzymes, e.g., ALT (ALT levels are considered a reliable marker for disease activity) but that fail to eradicate the virus do not cure the disease, because when therapy is stopped, the liver enzymes will again become abnormal if the virus is still present in the blood. The standard of measurement of hepatitis C in the blood is the test for hepatitis C virus RNA by PCR (polymerase chain reaction). PCR assays have sufficient sensitivity to detect 100 copies of virus per milliliter of blood.

Current treatment for hepatitis C generally is with various amounts of interferon  $\alpha$ , administered by injection, usually at a dose of about five million units, three times per week, for about six months in adults. This regimen has led to a cure rate (as measured by eradication of the virus) of only about 10-15%. There are several preliminary reports in the medical literature on small numbers of patients being treated with injections of interferon  $\alpha$  and ribavirin (an oral nucleoside analog with broad spectrum activity against viruses) in combination for 6 months. The dose of ribavirin used in these studies is generally about 800-1200 mg per day. These preliminary reports indicate a cure rate of about 50% in six months. In addition, when treatment is likely to be curative in an individual patient, the liver enzymes will frequently normalize at about the 8th to the 12th week of combination therapy.

A preliminary abstract (AASLD Abstracts, Hepatology Oct. 1994, Program Issue, Vol 20, No. 4, Pt. 2 Abstract No. 293) reported on a treatment combination of interferon  $\alpha$  and ofloxacin, a quinolone antibiotic, which resulted in the cure of six out of eight hepatitis C patients with subgroup 1b with six months of therapy.

Treatment of hepatitis C with amantadine hydrochloride alone has been reported (J.P. Smith et al., "Treatment of Chronic Hepatitis C with Amantadine Hydrochloride", Abstract from Annual Meetings of the American Gastroenterological Association and AASLD (1996)) with only 30% of patients having complete response; 40% of patients experienced a partial response, and 30% were not responsive to treatment.

One difficulty associated with interferon-based treatments for hepatitis C is the

high rate of undesirable side effects experienced by patients who receive interferon therapy. Interferon treatments are associated with fever, headache, fatigue and other "flu-like" symptoms in a significant number of patients receiving such treatments. The side effects can in some instances be severe, with the result that in some cases interferon therapy must be discontinued.

An additional disadvantage of interferon therapy is the need for frequent injections of interferon (generally subcutaneous (SC) or intramuscular (IM)), which can result in discomfort to the patient and possibly decrease patient compliance with therapy. Also, interferon therapy can be quite expensive.

New methods and compositions for the treatment of hepatitis C, with or without interferon, are needed.

#### Summary of the Invention

The present invention provides compositions and methods for treatment of hepatitis C infection. In general, the methods of the invention feature the use of a combination of drugs to treat chronic hepatitis C infection. In certain embodiments, the combination of drugs includes an interferon (such as interferon  $\alpha$ ), while in other embodiments, the combination of drugs does not include interferon (i.e., the combination of drugs is substantially interferon-free).

In one aspect, the invention features a method for treating a subject suffering from hepatitis C infection. In one embodiment, the method includes the step of administering to the subject a therapeutically effective amount of a combination of at least two agents selected from the group consisting of nucleoside analogs, quinolone antibiotics, and amantadine anti-viral agents; or pharmaceutically-acceptable salts thereof. Thus, in certain embodiments, the method includes the step of administering a nucleoside analog and a quinolone antibiotic; or a nucleoside analog and an amantadine anti-viral agent; or a quinolone antibiotic and an amantadine anti-viral agent. In certain embodiments, the nucleoside analog is ribavirin. In certain embodiments, the quinolone antibiotic is selected from the group consisting of levofloxacin, ofloxacin and ciprofloxacin. In certain embodiments, the amantadine anti-viral agent is rimantadine. In certain embodiments, the method drug combination further includes an interferon, more preferably interferon  $\alpha$ . In certain embodiments, the treatment is continued for at least about two months after the subject becomes PCR negative for hepatitis C virus. In preferred embodiments, the hepatitis C infection is cured, e.g., the hepatitis C virus is eradicated in the blood, e.g., as measured by PCR analysis. In preferred embodiments, interferon is not administered to the patient during the combination therapy.

In certain preferred embodiments, the combination comprises a nucleoside

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analog, a quinolone antibiotic, and an amantadine anti-viral agent. In certain preferred embodiments, the quinolone antibiotic is ofloxacin, levofloxacin or ciprofloxacin. In preferred embodiments, the amount of the nucleoside analog is 800-1200 mg per day; in more preferred embodiments, the nucleoside analog is administered in two or three divided doses each day. In preferred embodiments, the amount of quinolone antibiotic is 400-800 mg per day; in certain preferred embodiments, the quinolone antibiotic is administered in two divided doses daily. In a preferred embodiment, the amantadine anti-viral agent is administered in an amount of about 100-400 mg per day, preferably in 2 divided doses. In preferred embodiments, the subject is a mammal, more preferably a human.

In a particularly preferred embodiment, the invention provides a method for treating a subject suffering from hepatitis C infection, the method comprising administering to the subject a therapeutically effective amount of a combination of ribavirin, ofloxacin, and rimantadine, or pharmaceutically-acceptable salts thereof, such that hepatitis C infection is treated.

In still another aspect, the invention features a method for treating a subject suffering from hepatitis C infection by administering to the subject a therapeutically effective amount of a combination of an interferon, a nucleoside analog, and an agent selected from the group consisting of quinolone antibiotics and amantidine; or pharmaceutically acceptable salts thereof, such that hepatitis C infection is treated. In certain embodiments, the interferon is interferon  $\alpha$ . In certain embodiments, the nucleoside analog is ribavirin. In certain embodiments, the third agent is a quinolone antibiotic; in certain preferred embodiments, the quinolone antibiotic is selected from the group consisting of ofloxacin and ciprofloxacin. In certain embodiments, the third agent is amantidine. In certain embodiments, the treatment is continued for at least about two months after the subject becomes PCR negative for hepatitis C virus.

In another embodiment, the method comprises administering to the subject a therapeutically effective amount of a combination of an interferon, a nucleoside analog, and a quinolone antibiotic, such that the hepatitis C infection is treated. In preferred embodiments, the hepatitis C infection is cured, e.g., the hepatitis C virus is eradicated in the blood, e.g., as measured by PCR analysis. In certain preferred embodiments, the nucleoside analog is ribavirin. In certain preferred embodiments, the quinolone antibiotic is ofloxacin or ciprofloxacin. In preferred embodiments, the amount of interferon  $\alpha$  is 6-15 million units per week. In preferred embodiments, the interferon  $\alpha$  is administered in three divided doses. In preferred embodiments, the amount of the nucleoside analog is 800-1200 mg per day; in more preferred embodiments, the nucleoside analog is administered in two or three divided doses each day. In preferred

embodiments, the amount of quinolone antibiotic is 400-800 mg per day; in certain preferred embodiments, the quinolone antibiotic is administered in two divided doses daily. In preferred embodiments, the subject is a mammal, more preferably a human.

In a preferred embodiment, the invention provides a method for treating a subject suffering from hepatitis C infection, the method comprising administering to the subject a therapeutically effective amount of a combination of interferon  $\alpha$ , ribavirin, and ofloxacin, such that hepatitis C infection is treated.

In another aspect, the invention provides a method for treating a subject suffering from hepatitis C infection, the method comprising administering to the subject a therapeutically effective amount of a combination of an interferon, a nucleoside analog, and amantidine, such that hepatitis C infection is treated. In this embodiment, amantidine is preferably administered at a dose of about 100 mg to about 500 mg per day. In certain embodiments, a quinolone antibiotic can be employed in addition to the interferon, nucleoside analog, and amantidine. In preferred embodiments, the interferon is interferon  $\alpha$ . In preferred embodiments, the nucleoside analog is ribavirin. In preferred embodiments, the treatment is continued for at least about two months, more preferably more than three months, after the subject becomes PCR negative for hepatitis C virus.

In another aspect, the invention provides a composition comprising an interferon, a nucleoside analog, and a third agent selected from the group consisting of quinolone antibiotics and amantidine; or pharmaceutically acceptable salts thereof.

In another aspect, the invention provides a pharmaceutical composition comprising a therapeutically effective amount of a combination of an interferon, a nucleoside analog, and a third agent selected from the group consisting of quinolone antibiotics and amantidine; or pharmaceutically acceptable salts thereof; in a pharmaceutically acceptable carrier.

In another aspect, the invention provides a kit comprising a container of a combination of an interferon, a nucleoside analog, and a third agent selected from the group consisting of quinolone antibiotics and amantidine; or pharmaceutically acceptable salts thereof; and instructions for administering a therapeutically effective amount of the combination of the interferon, the nucleoside analog, and amantidine to a subject suffering from hepatitis C infection such that treatment of hepatitis C occurs.

In another aspect, the invention provides a composition comprising at least two agents selected from the group consisting of nucleoside analogs, quinolone antibiotics, and amantadine anti-viral agents; or pharmaceutically acceptable salts thereof.

In another aspect, the invention provides a pharmaceutical composition comprising a therapeutically effective amount of a combination of at least two agents

selected from the group consisting of nucleoside analogs, quinolone antibiotics, and adamantine anti-viral agents; or pharmaceutically acceptable salts thereof; in a pharmaceutically acceptable carrier.

In another aspect, the invention provides a kit comprising a container of a combination of at least two agents selected from the group consisting of nucleoside analogs, quinolone antibiotics, and adamantine anti-viral agents; or pharmaceutically acceptable salts thereof; and instructions for administering a therapeutically effective amount of the combination of the agents to a subject suffering from hepatitis C infection such that treatment of hepatitis C occurs.

Treatment according to the methods of the invention can result in rapid normalization of ALT levels, as well as nearly complete disappearance of the hepatitis C virus after only one month of treatment, and complete disappearance of the hepatitis C virus after thirteen weeks of treatment, as measured by quantitative PCR of viral RNA. The interferon-free treatment methods and compositions of the invention are generally less expensive than, and can be substantially as effective as, conventional interferon therapy.

In still another aspect, the invention provides a method for treating a subject suffering from hepatitis C while maintaining hematocrit in the subject. The method includes the step of administering to the subject a therapeutically effective amount of a nucleoside analog and erythropoetin; or pharmaceutically-acceptable salts thereof, such that treatment of hepatitis C infection occurs while maintaining hematocrit in the subject. In certain embodiments, the erythropoetin comprises epoetin alfa, which can be administered to the patient in doses of about 5000 units SC about three times per week.

#### Detailed Description of the Invention

The methods of the invention generally feature the use of combination drug therapy for the treatment of hepatitis C. In one aspect, the combination therapy involves the use of at least two agents selected from the group consisting of nucleoside analogs, quinolone antibiotics, and amantadine anti-viral agents. The invention provides therapies which are less expensive than interferon therapy, are often better tolerated by patients than interferon, and have results comparable or superior to conventional interferon therapies.

The term "interferon" is known in the art and refers to a family of proteins that modulate immune response and confer resistance to certain viral infections. The interferons include interferons  $\alpha$ ,  $\beta$  and  $\gamma$ . Another preferred interferon is consensus interferon (available from Amgen, Thousand Oaks, CA). In preferred embodiments, the interferon used in methods of the invention is interferon  $\alpha$ . However, other interferon

s(such as  $\beta$  or  $\gamma$ ) can be used in the inventive methods and compositions, provided that the interferon is active against hepatitis C (either alone or in combination with other drugs, e.g., as described herein). Activity against hepatitis C can be determined by *in vitro* or *in vivo* testing methods known in the art.

The term "nucleoside analog" is a term of art and refers to drugs which are analogs or derivatives of naturally-occurring nucleosides. In preferred embodiments, the nucleoside analog has anti-viral properties (e.g., against hepatitis C) without significant toxicity to a subject (e.g., a human) at therapeutically effective doses. In preferred embodiments, the nucleoside analog is ribavirin. However, other nucleoside analogs such as lamivudine (which has been shown to be active against hepatitis B), vidarabine, ganciclovir, and the like, can be employed in the current invention.

The term "quinolone antibiotic" is known in the art and refers to antibiotic drugs having the quinolone nucleus. Representative quinolone antibiotics include e.g., ofloxacin, levofloxacin, ciprofloxacin, norfloxacin, and the like. In preferred embodiments, the quinolone antibiotic is levofloxacin, ofloxacin or ciprofloxacin. In a most preferred embodiment, the quinolone antibiotic is ofloxacin.

The term "amantadine anti-viral agent," as used herein refers to an anti-viral agent structurally related to amantadine, including derivatives, analogs, and salts of amantadine. Preferred amantadine anti-viral agents include amantadine and rimantadine.

The phrase "therapeutically-effective amount" as used herein means that amount of a drug, material, combination or composition of the invention which is effective for producing some desired therapeutic effect upon administration to a subject, e.g., treatment of hepatitis C infection, including, e.g., normalization of liver enzymes and/or reduction of or eradication of viral RNA in blood.

The choice of appropriate dosages for the drugs used in combination therapy according to the invention can be determined and optimized by the skilled artisan, e.g., by observation of the patient; including the patient's overall health, the response to the combination therapy, and the like. A preferred dose for ribavirin is between about 400 mg-2000 mg daily. A preferred dose for lamivudine is from about 5 to about 1000 mg per day. A preferred dose for ofloxacin is from about 100 to about 1000 mg per day. A preferred dose for other quinolone antibiotics is generally in the range from about 100 to about 2000 mg per day. A preferred dose for amantadine is about 100-500 mg per day. In embodiments in which interferon is employed, preferred dose ranges for adults for interferon  $\alpha$  (or other interferons) are between about 2 million units weekly and 70 million units weekly injected subcutaneously (SC) or intramuscularly (IM), given either daily or 1-6 times per week.

In one aspect, the invention provides a method for treating a subject suffering from hepatitis C infection, the method comprising administering to the subject a therapeutically effective amount of a combination of at least two agents selected from the group consisting of nucleoside analogs, quinolone antibiotics, and amantadine anti-viral agents (i.e., at least one agent from two or more of the three classes of agents). In certain embodiments, amantadine is preferably administered at a dose of about 100 mg to about 500 mg per day, more preferably about 200 mg per day, preferably in two doses of 100 mg each. The amantadine can be administered in any of the forms, or by routes of administration, known in the art. Other amantadine analogs or derivatives (e.g., rimantadine) can be employed in combination with or in place of amantadine, if desired. In a particularly preferred embodiment, the method includes the step of administering to the subject a therapeutically effective amount of a combination of a nucleoside analog, a quinolone antibiotic, and an amantadine anti-viral agent. Thus, the invention contemplates the use of a combination of a nucleoside analog such as ribavirin, amantadine, and a quinolone antibiotic such as ofloxacin. In preferred embodiments, the invention contemplates the use of a combination of a nucleoside analog, an amantadine anti-viral agent, and a quinolone antibiotic, without the use of an interferon.

In another aspect, the combination therapy involves the use of an interferon, a nucleoside analog, and a third agent selected from the group consisting of quinolone antibiotics and amantidine.

In one embodiment, the invention provides a method for treating a subject suffering from hepatitis C infection, the method comprising administering to the subject a therapeutically effective amount of a combination of an interferon, a nucleoside analog, and amantidine. In this embodiment, amantidine is preferably administered at a dose of about 100 mg to about 500 mg per day, more preferably about 200 mg per day, preferably in two doses of 100 mg each. The amantidine can be administered in any of the forms, or by routes of administration, known in the art. Other amantidine analogs or derivatives (e.g., rimantidine) can be employed in combination with or in place of amantidine, if desired. In certain embodiments, a quinolone antibiotic can be employed in addition to the interferon, nucleoside analog, and amantidine. Thus, the invention contemplates the use of a combination of an interferon, a nucleoside analog, amantidine, and a quinolone antibiotic.

It will be understood by the skilled artisan that the therapeutic agents described herein can be administered separately, or, if appropriate, can be administered together, e.g., by injection of a solution which includes a therapeutically effective amount of a combination or composition as described herein, or administration of a pill which includes a drug combination as described herein; or pharmaceutically acceptable salts

thereof. A preferred route of administration is oral administration, preferably oral administration of a tablet, pill, capsule, or other suitable dosage form which includes a combination of drugs as described herein, e.g., a pill which includes both ribavirin and amantidine.

In general, the drugs should be administered initially one at a time for the first few days of therapy until it is determined that the patient is tolerating each drug before the next drug is added. The order in which the drugs are administered is not crucial; however, all drugs can, in preferred embodiments, be given together as soon as possible to prevent the hepatitis C virus from developing resistance to any part of the therapy. In certain embodiments in which interferon is employed, an interferon can be given alone for a time, e.g., 4 weeks, before the other drugs were started. For example a combination of the interferon and the nucleoside analog (e.g., ribavirin) can be administered for a period of time (e.g., from about 1 week to about 3 months, more preferably about 1 month to about two months) before the addition of the quinolone antibiotic or amantidine. In certain embodiments, a combination of a nucleoside analog (e.g., ribavirin) and an amantadine anti-viral agent (e.g., amantadine or rimantadine) can be administered for a period of time (e.g., from about 1 week to about 3 months, more preferably about 1 month to about two months) before the addition of a quinolone antibiotic. Use of these modified dosages regimen can permit the liver enzymes to remain at or near normal levels before administration of, e.g., amantadine. In certain embodiments, the invention features the combination administration of a nucleoside analog, a quinolone antibiotic, and an amantadine anti-viral agent for a period of up to 9 months, more preferably 12 months, or until the viral PCR test becomes negative (preferably until at least three months after the PCR becomes negative). In certain embodiments, the invention features the simultaneous administration of an interferon, a nucleoside analog, and a quinolone antibiotic for a period of up to 9 months, or until the viral PCR test becomes negative. In other embodiments, the invention features the simultaneous administration of an interferon, a nucleoside analog, and amantidine for a period of up to 9 months, or until the viral PCR test becomes negative.

The combination therapy of the invention will generally be administered until the viral PCR test becomes negative. In preferred embodiments, the combination therapy is administered for at least 2 weeks, more preferably at least 4 weeks, more preferably at least 2 months, most preferably for at least three months. In general, the therapy should be continued for a period of time after PCR assays indicate disappearance of the virus from blood (a negative PCR assay), to ensure that the virus has been eradicated from the body and will not return when therapy is discontinued. In preferred embodiments, the therapy is continued for at least one month after a negative PCR assay, more preferably

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at least about two months, at least about three months, at least about four months, or at least about eight months after negative PCR assay. However, in preferred embodiments, the combination therapy is administered for a period of no more than six months, in more preferred embodiments, for a period of no more than four months, after a negative PCR assay. The length of time the therapy should be continued after negative PCR assay can depend, at least in part, on the health of the subject, the tolerance of the subject for the combination therapy, the strain of hepatitis C virus being treated, and the like.

Several other techniques can be used to facilitate a rapid cure. It has been reported that interferon  $\alpha$  is most effective when the liver iron stores are minimized. Therefore, if the serum ferretin level (normal 10-200 ng/ml) is elevated or even if it is in the high normal range, phlebotomy can be performed to reduce the pre-treatment ferretin level, e.g., to less than 150ng/ml or less than 50ng/ml.

The addition of vitamins and antioxidant vitamins to the treatment regimen can also be beneficial, since there is evidence that certain vitamins can help the body to fight infections and viral infections. In general, the administration of a multivitamin and mineral preparation with beta carotene (about 10,000 units), vitamin C 300-2000 mg, vitamin E 200-2000 units, and one B-complex 100 with folic acid, is contemplated for use with the combination therapy of the invention. However, as noted above, in certain embodiments it is preferred that liver iron stored be minimized; thus, in a preferred embodiment, a multivitamin and mineral preparation should contain no iron. Patients can also be treated with phlebotomy, if necessary, either prior to or during drug therapy to reduce ferritin levels to less than 150 ng/ml.

The invention also contemplates the use of additional agents to counter the side effects of the combination therapy drugs used to eradicate the virus. The use of GCSF (granulocyte colony stimulating factor) in various doses to raise the white blood cell (WBC) or neutrophil counts has been reported. It is also known that treatment with interferon  $\alpha$  can cause the neutrophil count to drop below about 1000 cells/mcl. Thus, in a preferred embodiment, the neutrophil count is maintained in the range of 1000-4000 cells/mcl by the use of GCSF injections. A typical dose of GCSF can be about 300 mcg SC, preferably about 6-10 hours before each interferon  $\alpha$  injection. GCSF is preferably administered before the interferon  $\alpha$  because interferon  $\alpha$  is believed to work, at least in part, by increasing the activity of the white blood cells in fighting viral infection. By giving the GCSF before the interferon  $\alpha$ , more white blood cells can be circulating to be activated by the interferon  $\alpha$ . If GCSF prior to interferon therapy causes an increase in fevers, headaches, flu-like symptoms, that are common to interferon therapy, then the dose of interferon should be reduced to about 2.5-3 million units SC three times per

week, and the GCSF discontinued. The WBC and neutrophil counts should improve toward normal with reduction of the interferon dose even without GCSF. Platelet counts are preferably kept above 100,000/mcl by reducing the interferon dose if GCSF fails to improve the platelet count. The dose of GCSF can be adjusted to maintain normal neutrophil counts.

The invention further contemplates the use of epoetin alfa (erythropoetin) in conjunction with the combination therapy for treatment of hepatitis C infection. One of the side effects of the administration of ribavirin is a reversible hemolytic anemia. It has been reported that, in the use of ribavirin to treat hepatitis C infection, the dose of ribavirin has had to be reduced or eliminated due to hemolytic anemia. For example, in treatment of the patient described in Example 1, *infra*, the dose of ribavirin was reduced for about a week to 800 mg/day (from a full dose of 1200 mg/day) due to a sudden drop in the hematocrit from about 37 to 27. The drop in hematocrit was treated by the addition of epoetin alfa, about 5000 units SC three times per week (later reduced to one or two times per week). The patient was subsequently able to resume the full dose of ribavirin and the hematocrit returned to and stabilized in the mid 30's. Thus, the invention provides a method for treating a subject suffering from hepatitis C while maintaining hematocrit in the subject. The method includes the step of administering to the subject a therapeutically effective amount of a nucleoside analog and erythropoetin; or pharmaceutically-acceptable salts thereof, such that treatment of hepatitis C infection occurs while maintaining hematocrit in the subject. In certain embodiments, a drop in hematocrit due to ribavirin-induced reversible hemolytic anemia can be treated by the addition of epoetin alfa, about 5000 units SC three times per week.

Other agents can be used in conjunction with the combination therapy of the invention. For example, analgesics such as acetaminophen may be used to treat headaches that can also be a side effect of some of the medications. In embodiments in which interferon is employed, antidepressants may be needed to offset the depression which is known to complicate interferon  $\alpha$  therapy.

As will be apparent to the skilled artisan, careful monitoring of the patient is needed to monitor the hematocrit (e.g., for sudden drops that may be caused by ribavirin). Liver enzymes and chemistry profile as well as CBC (complete blood count) with WBC differential (to monitor platelet, neutrophil and WBC counts) should preferably be performed initially and weekly for about the first 6 weeks of therapy, then, if stable, for every 2 weeks thereafter. Hepatitis C viral RNA by PCR, quantitative, is preferably performed at the start of therapy and about monthly thereafter. Therapy can be discontinued when the PCR test is negative, although, as described above, it is generally preferable to continue therapy even after a negative PCR assay, to ensure the

eradication of the virus from the patient's body. The patient should also be monitored weekly by history and physical to watch for signs of depression, compliance with treatment regimen, signs of allergies, and the like. The patient should be told to call the doctor at the first signs of itchiness or a rash since quinolones can cause serious allergic reactions. If a rash appears, the quinolone is preferably discontinued immediately and antihistamines given. Other therapeutic agents (e.g., interferons, nucleoside analogs or adamantine anti-viral agents) can be continued as long as the rash resolves upon discontinuance of the quinolone and use of the antihistamine.

Treatment should be continued at least until the hepatitis C viral RNA by PCR is negative. If a serious side effect occurs which cannot be tolerated or effectively controlled, the treatment should generally be stopped. Treatment can be continued for up to nine months or up to twelve months, if necessary.

In another aspect, the invention provides compositions useful for the treatment of hepatitis C. In general, the compositions include at least two agents selected from the group consisting of nucleoside analogs, quinolone antibiotics, and adamantine anti-viral agents. In a preferred embodiment, the composition is substantially free of interferon. In one embodiment, the invention provides a composition comprising a nucleoside analog, a quinolone antibiotic, and an adamantine anti-viral agent; or pharmaceutically acceptable salts thereof. In another embodiment, the composition comprises a nucleoside analog and a quinolone antibiotic; or pharmaceutically acceptable salts thereof. In another embodiment, the invention provides a nucleoside analog, and an adamantine anti-viral agent, or pharmaceutically acceptable salts thereof. In yet another embodiment, the invention provides a quinolone antibiotic, and an adamantine anti-viral agent, or pharmaceutically acceptable salts thereof.

In other embodiments, a composition of the invention can comprise an interferon, a nucleoside analog, and a third agent selected from the group consisting of quinolone antibiotics and amantidine; or pharmaceutically acceptable salts thereof. In one embodiment, the composition comprises an interferon, a nucleoside analog, and a quinolone antibiotic; or pharmaceutically acceptable salts thereof. In another embodiment, the invention provides a composition comprising an interferon, a nucleoside analog, and amantidine, or pharmaceutically acceptable salts thereof. In preferred embodiments, the amounts of the respective drug components are selected such that the composition is effective for treatment of a patient suffering from hepatitis C infection.

In preferred embodiments, the amounts of the respective drug components are selected such that the composition is effective for treatment of a patient suffering from hepatitis C infection. The compositions of the invention can in addition include such

other therapeutic agents as are described herein.

In another embodiment, the invention provides (preferably non-toxic) pharmaceutical compositions for treating a patient suffering from hepatitis C infection. In general, the pharmaceutical compositions include at least two agents selected from the group consisting of nucleoside analogs, quinolone antibiotics, and adamantane anti-viral agents. In a preferred embodiment, the pharmaceutical composition is substantially free of interferon. In one embodiment, the pharmaceutical composition comprises a therapeutically effective amount of a combination of a nucleoside analog, a quinolone antibiotic, and an adamantane anti-viral agent; or pharmaceutically acceptable salts thereof; in a pharmaceutically acceptable solvent. In another embodiment, the pharmaceutical composition comprises a therapeutically effective amount of a combination of a nucleoside analog and a quinolone antibiotic, or pharmaceutically acceptable salts thereof, in a pharmaceutically acceptable carrier. In another embodiment, the pharmaceutical composition comprises a therapeutically effective amount of a combination of a nucleoside analog, and an adamantane anti-viral agent, or pharmaceutically acceptable salts thereof, in a pharmaceutically acceptable carrier. In yet another embodiment, the pharmaceutical composition comprises a therapeutically effective amount of a combination of a quinolone antibiotic and an adamantane anti-viral agent, or pharmaceutically acceptable salts thereof, in a pharmaceutically acceptable carrier.

In other embodiments, the pharmaceutical composition of the invention comprises a therapeutically effective amount of a combination of an interferon, a nucleoside analog, and a third agent selected from the group consisting of quinolone antibiotics and amantidine; or pharmaceutically acceptable salts thereof; in a pharmaceutically acceptable solvent. In one embodiment, the pharmaceutical composition comprises a therapeutically effective amount of a combination of an interferon, a nucleoside analog, and amantidine, or pharmaceutically acceptable salts thereof, in a pharmaceutically acceptable carrier. In another embodiment, the pharmaceutical composition comprises a therapeutically effective amount of a combination of an interferon, a nucleoside analog, and a quinolone antibiotic, or pharmaceutically acceptable salts thereof, in a pharmaceutically acceptable carrier.

The pharmaceutical compositions of the invention can further include solvents, excipients, diluents, flavorings, and other additives such as conventional in formulation of pharmaceuticals. The invention contemplates the use of oral dosage forms such as tablets, and other solid dosage forms of the pharmaceutical compositions of the present invention, such as dragees, capsules, pills and granules, optionally scored or prepared with coatings and shells, such as enteric coatings and other coatings well known in the

pharmaceutical-formulating art.

In still another aspect, the invention provides kits for treatment of hepatitis C infection. In some embodiments, the kit is substantially free of interferon. In one embodiment, the kits include a container including a combination of for at least two agents selected from the group consisting of nucleoside analogs, quinolone antibiotics, and adamantane anti-viral agents. In another embodiment, the kit of the invention comprises a container of a nucleoside analog, a container of a quinolone antibiotic, and a container of an adamantane anti-viral agent; or pharmaceutically acceptable salts thereof, and instructions for administering a therapeutically effective amount of a combination of the nucleoside analog, the quinolone antibiotic, and the adamantane anti-viral agent to a subject suffering from hepatitis C infection such that treatment of hepatitis C occurs. In another embodiment, the kit comprises a container of a nucleoside analog, and a container of an adamantane anti-viral agent, or pharmaceutically acceptable salts thereof, and instructions for administering a therapeutically effective amount of a combination of the nucleoside analog, and the adamantane anti-viral agent to a subject suffering from hepatitis C infection such that treatment of hepatitis C occurs. In another embodiment, the kit comprises a container of a combination of a nucleoside analog and a container of a quinolone antibiotic, or pharmaceutically acceptable salts thereof, and instructions for administering a therapeutically effective amount of a combination of the nucleoside analog and the quinolone antibiotic to a subject suffering from hepatitis C infection such that treatment of hepatitis C occurs. In another embodiment, the kit comprises a container of a quinolone antibiotic, a container of an amantadine anti-viral agent, or pharmaceutically acceptable salts thereof, and instructions for administering a therapeutically effective amount of a combination of the quinolone antibiotic, and the amantadine anti-viral agent to a subject suffering from hepatitis C infection such that treatment of hepatitis C occurs.

In other embodiments, the kits of the invention comprise an interferon, a nucleoside analog, and a third agent selected from the group consisting of quinolone antibiotics and an amantidine anti-viral agent; or pharmaceutically acceptable salts thereof. In one embodiment, the kit comprises a container of an interferon, a container of a nucleoside analog, a container of a quinolone antibiotic, or pharmaceutically acceptable salts thereof, and instructions for administering a therapeutically effective amount of a combination of the interferon, the nucleoside analog, and the quinolone antibiotic to a subject suffering from hepatitis C infection such that treatment of hepatitis C occurs. In another embodiment, the kit comprises a container of a combination of an interferon, a nucleoside analog, and a quinolone antibiotic, or pharmaceutically acceptable salts thereof, and instructions for administering a therapeutically effective

amount of the combination of the interferon, the nucleoside analog, and the quinolone antibiotic to a subject suffering from hepatitis C infection such that treatment of hepatitis C occurs. In another embodiment, the kit comprises a container of an interferon, a container of a nucleoside analog, a container of amantidine, or pharmaceutically acceptable salts thereof, and instructions for administering a therapeutically effective amount of a combination of the interferon, the nucleoside analog, and amantidine to a subject suffering from hepatitis C infection such that treatment of hepatitis C occurs. In another embodiment, the kit comprises a container of a combination of an interferon, a nucleoside analog, and amantidine, or pharmaceutically acceptable salts thereof, and instructions for administering a therapeutically effective amount of the combination of the interferon, the nucleoside analog, and amantidine to a subject suffering from hepatitis C infection such that treatment of hepatitis C occurs.

In still another embodiment, the invention provides a method for treating a subject suffering from hepatitis C while maintaining hematocrit in the subject. The method includes the step of administering to the subject a therapeutically effective amount of a nucleoside analog and erythropoetin; or pharmaceutically-acceptable salts thereof, such that treatment of hepatitis C infection occurs while maintaining hematocrit in the subject.

#### Example 1

A 40-year-old woman suffering from hepatitis C infection was treated with interferon  $\alpha$ , ribavirin, and ofloxacin combination therapy according to the invention. A quantitative PCR blood test (Specialty Laboratories, Santa Monica, CA) performed before the start of therapy showed the presence of hepatitis C viral RNA at 7.9 pg/ml, indicating hepatitis C infection. The doses of drugs were as follows: interferon  $\alpha$ , 5 million units three times per week; ribavirin, 1200 mg per day (in two divided doses); and ofloxacin, 600 mg per day (in two divided doses). After 2 weeks, a skin rash developed, and ofloxacin was discontinued. Ciprofloxacin (1000 mg per day in two divided doses) was substituted for the ofloxacin at 11 weeks of therapy. After 3 weeks, the hematocrit dropped from 37 to 27, and the dose of ribavirin was reduced to 800 mg per day. Erythropoetin therapy was begun (5000 units SC three times per week), with the result that the hematocrit returned to a stable level (33) after two weeks. The ribavirin dose was then returned to 1200 mg per day. At week 10 of treatment, the interferon  $\alpha$  dose was reduced to 2.5 million units three times per week.

After five weeks of therapy, the quantitative PCR test indicated a viral RNA level of less than 0.5 pg/ml, although the presence of viral RNA was noted. After 13 weeks of therapy, the quantitative PCR test indicated that no hepatitis C viral RNA was

present in the blood.

In addition to the patient described above, four other patients have been treated with the combination therapy of the invention (in which interferon  $\alpha$  and ribavirin were together administered for one to two months before addition of ofloxacin to the treatment regime), and all four patients became PCR negative for the hepatitis C virus.

#### Example 2

Five patients suffering from hepatitis C infection (Type 1b) were treated with the following regimen: interferon  $\alpha$ , 3-5 million units SC, three times per week; ribavirin, 800-1200 mg per day orally; levofloxacin, 500 mg per day orally; and amantidine, 200 mg per day orally. All five patients achieved normal liver enzyme levels. Three of the five patients became PCR negative after less than six months of treatment and appeared to be cured.

Six patients infected with non-Type 1b hepatitis C were treated with the same four-drug combination (interferon  $\alpha$ , ribavirin, levofloxacin, and amantidine). After five months of treatment, all six patients had normal liver enzymes and were PCR negative.

#### Example 3

A 46-year-old man suffering from hepatitis C infection (Type 1B) was treated with a combination therapy according to the invention. The patient had previously received an interferon-based combination therapy, but had experienced only partial response, as indicated by persistence of virus in the blood. The patient's viral count at the start of the interferon-based therapy was greater than 5,000,000 copies/ml. The patient initially received treatment with interferon  $\alpha$ ; ribavirin and ofloxacin. A quantitative PCR blood test (NGI, Culver City, CA) performed after five months of the interferon-based therapy showed the presence of hepatitis C viral RNA at a level of 4,600,000 copies/ml, indicating that hepatitis C infection persisted. In addition, during the interferon therapy the patient had experienced side effects believed due to interferon, including depression, headaches, fever, and chills.

Interferon therapy was discontinued and the patient was treated with an interferon-free combination of drugs according to the present invention. The doses of drugs were as follows: ribavirin, 1200 mg per day (in three 400 mg doses); ofloxacin, 600 mg per day (in two 300 mg doses); and rimantadine, 200 mg per day (in two 100 mg doses). All drugs were administered orally. Lopid (gemfibrozil, 600 mg twice daily) was administered to lower the patient's high (1000 mg/dl) serum triglyceride level.

After 2 weeks of the interferon-free combination therapy, the level of hepatitis C RNA in the blood had fallen to 700,000 copies/ml, a reduction of over 80%. In addition,

the ALT levels fell from 26 U/L to 18 U/L. The patient tolerated the interferon-free combination therapy better than the previous interferon therapy, as indicated by a decrease in liver enzymes, headaches, fever, chills, and depression.

An additional patient were treated with the three-drug interferon-free regimen described above. This patient (suffering from Type 1b infection) and showed an initial response to the interferon-free three-drug therapy, including normalization of liver enzymes and decline in viral titer. Subsequently, interferon  $\alpha$  was added to the therapy for this patient after about two months, with the result that he became PCR negative.

Example 4

A 43 year old white male suffering from hepatitis infection was treated with an interferon-free combination therapy of the invention. The patient had not previously received any interferon-based therapy. Treatment was begun with ribavirin, 1200 mg per day (in three 400 mg doses); levofloxacin, 500 mg per day; and rimantadine, 200 mg per day (in two 100 mg doses). After one month of treatment, the patient's ALT levels had normalized and PCR assays showed a marked suppression of hepatitis C virus in the blood, which was maintained at three months.

Thus, the interferon-free therapies of the invention can provide excellent response, even in patients suffering from infection by relatively refractory viral strains (such as Type 1B).

Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, numerous equivalents to the specific procedures described herein. Such equivalents are considered to be within the scope of this invention and are covered by the following claims.

The contents of all references cited herein are hereby incorporated by reference.

Other embodiments are within the following claims.

What is claimed is:

1. A method for treating a subject suffering from hepatitis C infection, the method comprising the step of administering to the subject a therapeutically effective amount of at least two compounds selected from the group consisting of nucleoside analogs, quinolone antibiotics, and amantadine anti-viral agents; or pharmaceutically-acceptable salts thereof, such that treatment of hepatitis C infection occurs.
2. The method of claim 1, wherein the method comprises administering to the subject a nucleoside analog, a quinolone antibiotic, and an amantadine anti-viral agent.
3. The method of claim 2, wherein the nucleoside analog is ribavirin.
4. The method of claim 2, wherein the quinolone antibiotic is selected from the group consisting of ofloxacin, ciprofloxacin and levofloxacin.
5. The method of claim 2, wherein the amantadine anti-viral agent is rimantadine.
6. The method of claim 1, wherein the treatment is continued for at least about two months after the subject becomes PCR negative for hepatitis C virus.
7. The method of claim 1, wherein the at least two compounds are substantially free of interferon.
8. The method of claim 1, wherein the method further comprises administering an interferon to the subject.
9. The method of claim 8, wherein the interferon is interferon  $\alpha$  or consensus interferon.
10. A method for treating a subject suffering from hepatitis C infection, the method comprising administering to the subject a therapeutically effective amount of a composition comprising ribavirin, ofloxacin, and rimantadine, or pharmaceutically-acceptable salts thereof, such that hepatitis C infection is treated.
11. The method of claim 10, wherein the combination of ribavirin, ofloxacin, and rimantadine is substantially free of interferon.

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12. The method of claim 10, wherein the composition further comprises interferon  $\alpha$ .
13. A composition comprising at least two compounds selected from the group consisting of nucleoside analogs, quinolone antibiotics, and amantadine anti-viral agents; or pharmaceutically acceptable salts thereof, wherein the composition is substantially free of interferon.
14. A pharmaceutical composition comprising a therapeutically effective amount of at least two compounds selected from the group consisting of nucleoside analogs, quinolone antibiotics, and amantadine anti-viral agents; or pharmaceutically acceptable salts thereof; in a pharmaceutically acceptable carrier;  
wherein the pharmaceutical composition is substantially free of interferon.
15. A kit comprising a container of a composition comprising at least two compounds selected from the group consisting of nucleoside analogs, quinolone antibiotics, and amantadine anti-viral agents; or pharmaceutically acceptable salts thereof; and instructions for administering a therapeutically effective amount of the composition to a subject suffering from hepatitis C infection such that treatment of hepatitis C occurs;  
wherein the composition is substantially free of interferon.
16. A composition comprising an interferon, a nucleoside analog, and an agent selected from the group consisting of quinolone antibiotics and amantidine; or pharmaceutically acceptable salts thereof.
17. The composition of claim 16, wherein the agent is a quinolone antibiotic.
18. The composition of claim 16, wherein the agent is amantidine.
19. A pharmaceutical composition comprising a therapeutically effective amount of a combination of an interferon, a nucleoside analog, and an agent selected from the group consisting of quinolone antibiotics and amantidine; or pharmaceutically acceptable salts thereof, in a pharmaceutically acceptable carrier.
20. A kit comprising a container of a combination of an interferon, a nucleoside analog, and an agent selected from the group consisting of quinolone antibiotics and amantidine; or pharmaceutically acceptable salts thereof; and instructions for

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administering a therapeutically effective amount of the combination to a subject suffering from hepatitis C infection such that treatment of hepatitis C occurs.

21. A method for treating a subject suffering from hepatitis C while maintaining hematocrit in the subject, the method comprising the step of administering to the subject a therapeutically effective amount of a nucleoside analog and erythropoetin; or pharmaceutically-acceptable salts thereof, such that treatment of hepatitis C infection occurs while maintaining hematocrit in the subject.

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## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(21) International Application Number: PCT/US97/19763		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).	
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(71)(72) Applicant and Inventor: NAJARIAN, Thomas [US/US]; 18 Mannix Circle, Belmont, MA 02178 (US).			
(74) Agents: DECONTI, Giulio, A., Jr. et al.; Lahive & Cockfield, LLP, 28 State Street, Boston, MA 02109 (US).		<b>Published</b> <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>	
		(88) Date of publication of the international search report: 13 August 1998 (13.08.98)	

**(54) Title:** COMBINATION THERAPY OF HEPATITIS C INFECTIONS**(57) Abstract**

Methods and compositions useful for treatment of hepatitis C infection are disclosed. In general, the compositions comprise a composition comprising at least two compounds selected from the group consisting of a nucleoside analog, a quinolone antibiotic, and an amantadine anti-viral agent. The compositions or drug combinations can optionally include an interferon, such as interferon  $\alpha$ . Pharmaceutical compositions and kits including the compositions of the invention are also disclosed.

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# INTERNATIONAL SEARCH REPORT

Int'l. Application No

PCT/US 97/19763

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61K31/495 A61K31/41 A61K31/13 A61K38/28  
 // (A61K31/495, 31:41, 31:13), (A61K31/495, 31:41), (A61K31/495, 31:13),  
 (A61K31/41, 31:13)

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category <sup>o</sup>	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	BRACONIER J H ET AL: "COMBINED ALPHA-INTERFERON AND RIBAVIRIN TREATMENT IN CHRONIC HEPATITIS C: A PILOT STUDY" SCANDINAVIAN JOURNAL OF INFECTIOUS DISEASES, vol. 27, no. 4, 1995, pages 325-329, XP000600916 see abstract see p. 328, "Discussion" ---	1-20
Y	EP 0 707 855 A (SCHERING CORP) 24 April 1996 see the whole document ---	1-20 -/-

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

### <sup>o</sup> Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
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1

Date of the actual completion of the international search

3 March 1998

Date of mailing of the international search report

12.06.98

### Name and mailing address of the ISA

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## INTERNATIONAL SEARCH REPORT

International Application No

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	BRILLANTI S ET AL: "A PILOT STUDY OF COMBINATION THERAPY WITH RIBAVIRIN PLUS INTERFERON ALFA FOR INTERFERON ALFA-RESISTANT CHRONIC HEPATITIS C" GASTROENTEROLOGY, vol. 107, no. 3, September 1994, pages 812-817, XP000600924 see abstract	1-20
P,Y	SMITH J P: "Treatment of chronic hepatitis C with amantadine." DIGESTIVE DISEASES AND SCIENCES, vol. 42, no. 8, August 1997, USA, pages 1681-1687, XP002057488 see abstract see page 1686, left-hand column, line 2-6	1-20
Y	SMITH J P: "Treatment of chronic hepatitis C with amantadine -hydrochloride." 96TH ANNUAL MEETING OF THE AMERICAN GASTROENTEROLOGICAL ASSOCIATION AND THE DIGESTIVE DISEASE WEEK, SAN FRANCISCO, CALIFORNIA, USA, MAY 19-22, 1996. GASTROENTEROLOGY 110 (4 SUPPL.). 1996. A1330. ISSN: 0016-5085, XP002057489 see abstract	1-20
P,Y	KOMATSU M ET AL: "Pilot study of ofloxacin and interferon-alpha combination therapy for chronic hepatitis C without sustained response to initial interferon administration." CANADIAN JOURNAL OF GASTROENTEROLOGY, vol. 11, no. 6, September 1997, pages 507-511, XP002057490 see the whole document	1-20
Y	TSUTSUMI, MIKIHIRO ET AL: "Effects of combination therapy with interferon and ofloxacin on chronic type C hepatitis: A pilot study" J. GASTROENTEROL. HEPATOL. (1996), 11(11), 1006-1011 CODEN: JGHEEO;ISSN: 0815-9319, XP002057491 see abstract	1-20

**INTERNATIONAL SEARCH REPORT**

application No.

PCT/US 97/19763

**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
  
2.  Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
  
3.  Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

See separate sheet

1.  As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
  
2.  As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
  
3.  As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
  
4.  No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1 - 20

**Remark on Protest**

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

**FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210**

**1. Claims: 1-20**

Use of at least two compounds selected from the group nucleoside analogues(such as ribavirin), quinolone antibiotic (such as ofloxacin etc), and amantidine anti-viral agents (such as rimantadine) in the treatment of hepatitis C infections

**2. Claim : 21**

Use of a nucleoside analogue together with erythropoetin in the treatment of hepatitis C

INTERNAL

## SEARCH REPORT

Information on patent family members

Int'l Application No

PCT/US 97/19763

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP 0707855 A	24-04-96	AU 5919296 A		29-11-96

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(21) International Application Number: PCT/US97/19763		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).
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(71)(72) Applicant and Inventor: NAJARIAN, Thomas [US/US]; 18 Mannix Circle, Belmont, MA 02178 (US).		(88) Date of publication of the international search report: 13 August 1998 (13.08.98)
(74) Agents: DECONTI, Giulio, A., Jr. et al.; Lahive & Cockfield, LLP, 28 State Street, Boston, MA 02109 (US).		

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AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakhstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		